REMARKS

Please add claims 83-85 as indicated in the listing of claims. Subsequent to the entry of this amendment, claims 58 and 80-85 will be pending and at issue. These additions add no new matter as the claim language is fully supported by the specification and original claims.

Applicant submits that the pending claims are in condition for allowance, and respectfully requests that the claims as amended be entered.

Applicants wish to thank the Examiner for withdrawing the previous rejection of claims 58 and 69 under 35 U.S.C. §102(e).

Applicants wish to thank the Examiner for withdrawing the previous rejection of claims 58 and 69-70 under 35 U.S.C. §103(a).

Applicants wish to thank the Examiner for withdrawing the previous rejection of claims 58 and 80-82 under 35 U.S.C. §103(a).

Rejection under 35 U.S.C. §103

Applicants respectfully traverse the rejection of claim 58 under 35 U.S.C. §103(a) as allegedly being unpatentable over Vigne et al.(US Patent 6,455,314) in view of Hallenbeck et al. (US Pub No.: 2002/0137213).

The Office Action alleges that Applicants previously failed to specifically and distinctly identify which particular elements of base claim 58 were allegedly missing from the combined teachings of the references. Applicants assert for reasons of record and below that the references alone or in combination do not teach all of the elements of the claim 58. Claim 58 requires an adenoviral particle comprising a modification to a fiber shaft protein, "wherein the modification is a mutation, insertion or replacement of at least one amino acid in a fiber shaft β-repeat corresponding to the last full β repeat, and wherein the fiber further comprises a modification in the AB loop or the CD loop of the fiber knob, wherein the fiber knob modification is selected from the group consisting of K01 and K012, whereby binding of the modified fiber or of a viral particle containing such modified fiber to the Coxsackie-Adenovirus Receptor (CAR) is reduced as compared to the unmodified fiber". Vigne does not teach or suggest a modified adenovirus

fiber in which the modification is in the last full β repeat, wherein binding of the modified fiber to CAR is reduced. Additionally the Examiner has previously recognized that Vigne does "not specifically describe fiber knob modifications to the AB or CD loop." (Page 7, 11/28/07 Office Action). Vigne describes large deletions or substitutions involving all or most of the Ad5 fiber shaft protein. For example, Vigne describes viruses having modified Ad5 fibers in which large portions of the fiber shaft (*i.e.*, repeats 4-16 or repeats 4-19, termed viruses "vBS1" and "vBS2", respectively) are deleted, but the native last full repeat is left intact. Alternatively, Vigne demonstrated a substitution of the entire Ad5 fiber shaft with the fiber shaft of Ad3 (termed "vBI1"). Vigne showed that viral productivity was reduced in each case for viruses harboring these fiber shaft alterations and suggests that the observed reduction in productivity is likely due to an inability of the modified fibers to interact efficiently with its cellular receptor. However, reduced binding to CAR appears to have only been demonstrated for the vBS1 deletion mutant. Assuming, *arguendo*, that CAR binding was reduced in the mutants, the skilled artisan would conclude that the region responsible for reducing CAR binding would likely be within the region of the Ad5 fiber shaft protein removed or replaced common to all of the mutants (i.e., repeats 4-16). Therefore, Vigne only shows large deletions or substitutions involving all or most of the shaft protein. Additionally, Hallenbeck is presented in regards to fiber knob modifications and does not teach or suggest a modified adenovirus fiber in which the modification is in the last full β repeat, wherein binding of the modified fiber to CAR is reduced.

It is further submitted the references provide no motivation to combine them nor would the skilled artisan have had a reasonable expectation of success in achieving an adenovirus particle of the present claims because Vigne teaches away from adenovirus particles having the recited fiber shaft modification.

As such, the teachings of both Vigne and Hallenbeck do not teach or suggest all of the recited claim limitations, do not supply a motivation to combine the cited references, and do not provide an expectation of success in achieving the present compositions. Accordingly, Applicants respectfully submit that a *prima facie* case of obviousness has not been established for the claimed invention, and request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 58 and 80-82 under 35 U.S.C. §103(a) as allegedly being unpatentable over Vigne et al.(US Patent 6,455,314) in view of Hallenbeck et al. (US Pub No.: 2002/0137213) and further in view of Havenga et al. (US Pub No.: 2003/0017138).

The Office Action alleges that Vigne teaches the targeted adenovirus vectors for delivery of heterologous genes, wherein modification of the internal sites of the adenovirus fiber protein that include short targeting peptides fused to the C-terminus of the fiber protein, or the fiber HI loop (knob) target the modified adenoparticles to specific cell types (Title and Abstract). Specifically disclosing that the fiber protein can be modified to have a fiber shaft that is shorter than a wild-type fiber shaft, in particular by an in-frame deletion or by replacing it with the shaft from another serotype(column 6). Additionally disclosing substitution or replacement of the Ad5 shaft with Ad3, comprising a modification in the last full repeat of the fiber shaft (column 33). Vigne further describe replacement of a part of the fiber 1-11 loop(knob) with a ligand peptide or targeting sequence, that impair the native entry pathway and provide an additional, CAR-independent, pathway of infection.(columns 47 and 48). With respect to modification of the last full repeat, Vigne teach the fiber shaft as comprising pseudorepeats of 15 amino acids, which are believed to form two alternating ß-strands and ß-bends; and that the overall length of the fiber shaft and the number of repeats varies between different adenoviral serotypes (column 2, lines 22-30). Vigne further teach that the fiber protein can be modified to have a fiber shaft that is shorter from another serotype (column 6). Additionally teaching using SOE35Kg primer corresponding to the last repeat of the Ad3 fiber shaft and primers that include modification resulting in the creation of restriction sites to generate an intertypic fiber composed of the Ad5 tail, the Ad3 shaft and part of the Ad5 knob, and flanked with unique restriction sites (column 31 and 32). The disclosed mutation thus encompasses a substitution or replacement of the Ad5 shaft with Ad3, comprising a modification in the last full repeat of the fiber shaft.

The Office Action alleges that Hallenbeck describe adenovirus particles mutated in their fiber proteins that no longer bind to their natural cellular receptor and can be retargeted to a specific cell type through the addition of a ligand to the virus capsid (Abstract). The Office Action

further alleges that Hallenbeck specifically describes adenoviral constructs containing the K01 fiber AB loop mutation (Fig. 9), displaying a diminished interaction with CAR (paragraph [0092]). Additionally the Action alleges that adenoviral vectors containing the K01 mutation in conjunction with a ligand targeting moiety are described in Example 3. The Examiner recognizes that Vigne and Hallenbeck do not describe the serotype D Ad37 virus having the sequence of SEQ ID NO:48 but alleges that Havenga cures this by teaching that Sequence 31 of Havenga comprises the last full repeat claimed in SEQ ID NO: 48. According to the Office Action, one of skill in the art would have been motivated to combine the teachings of Vigne, Hallenbeck and Havenga to substitute or modify the last full repeat of the fiber shaft of a serotype 37 in a retargeted adenoviral vector and been motivated to introduce a modification in the fiber shaft as taught by both Vigne and Havenga because such mutations provide an additional CAR-independent pathway of infection for adenovirus retargeting.

Applicants submit that even if one of skill in the art would have combined Vigne and Hallenbeck in view of Havenga, the resulting composition would not result in the adenoviral particle comprising a modification to a fiber shaft protein, wherein the modification is a mutation, insertion or replacement of at least one amino acid in a fiber shaft β-repeat corresponding to the last full β repeat, and wherein the fiber further comprises a modification in the AB loop or the CD loop of the fiber knob, wherein the fiber knob modification is selected from the group consisting of K01 and K012, whereby binding of the modified fiber or of a viral particle containing such modified fiber to the Coxsackie-Adenovirus Receptor (CAR) is reduced compared to the unmodified fiber. The Action alleges that Vigne and Havenga teach the fiber shaft modifications and Hallenbeck teaches the fiber knob modifications. As described above and argued previously Vigne does not teach the fiber shaft modification corresponding to the last full targeting a specific portion of the fiber to modify (i.e. the last full β repeat). Rather, Vigne teaches large deletions or substitutions involving all or most of the Ad5 fiber shaft protein which may additionally comprise all or a portion of a last full β repeat but doest not target the specific last full β repeat portion of the fiber to modify. Because of this, Vigne actually teaches away from focusing on modifying the last full β repeat. The Office Action additionally cites Havenga to attempt to bolster their argument, but Havenga also focuses on a large deletion or substitution

not focused on the last full β repeat. The specific example provided as Sequence 31 from Havenga comprises 381 amino acids of the Ad 37 protein. Whereas, the 16 amino acids associated with SEQ ID NO: 48 of the present invention is an example of a modification of a last full β repeat claimed in the present invention. Therefore, neither reference specifically teaches the targeting of the last full β repeat for modifying the fiber. Additionally, Hallenbeck only relates to the fiber knob modifications and does not cure the shortcomings of Vigne and Havenga. The Action alleges that the substitution or modification of the last full repeat of the fiber shaft of a serotype 37 in a retargeted adenoviral vector is obvious in light of the teachings of Vigne, Hallenbeck and Havenga. However as stated, none of the references mentions or exemplifies a targeted substitution of the last full repeat of the fiber shaft. The Action has equated the full or large sequence substitutions of general adenoviral proteins as shown in the art with targeting a specific portion of the fiber to modify (i.e. the last full β repeat) in an identified adenoviral particle.

As such, the teachings of Vigne and Hallenbeck in view of Havenga do not teach or suggest all of the recited claim limitations, do not supply a motivation to combine the cited references, and do not provide an expectation of success in achieving the present compositions. Accordingly, Applicants respectfully submit that a *prima facie* case of obviousness has not been established for the claimed invention, and request withdrawal of the rejection.

Conclusion

In view of the foregoing amendments and the remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this case.

The Commissioner is hereby authorized to charge $130.00 as payment for the Petition for One-Month Extension of Time. Additionally, the Commissioner is hereby authorized to charge any fees that may be due, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: May 29, 2009

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